American Journal of Medical Genetics 62:16–22 (1996)

Lethal Familial Fetal Akinesia Sequence (FAS) With Distinct Neuropathological Pattern: Type III Lissencephaly Syndrome

Férechté Encha Razavi, Jeanne Claudie Larroche, Joëlle Roume, Marie Gonzales, Helen C. Kondo, and Nicole Mulliez

Service Histo-Embryologie, Hôpital Henri Mondor (F.E.R., H.C.K.), Créteil, INSERM (U 29) Hôpital Port Royal (J.C.L.), and Laboratoire de Foetopathologie, Hôpital Saint Antoine (J.R., M.G., N.M.), Paris, France

We report on a distinct pattern of primary central nervous system (CNS) degeneration affecting neuronal survival in the brain and spinal cord in 5 fetuses with fetal akinesia sequence (FAS). This neuropathological pattern is characteristic of a lethal entity that we propose calling type III lissencephaly syndrome. Parental consanguinity and the recurrence in sibs support a genetic cause. The mechanism of neuronal death is not yet understood; abnormal apoptosis and/or deficiency in neurotropic factors may be considered possible causes.

KEY WORDS: **fetus, central nervous system, primary neuronal degeneration, microcephaly, brain atrophy, lissencephaly, fetal akinesia sequence, Neu-Laxova syndrome, Pena-Shokeir phenotype, type III lissencephaly syndrome**

INTRODUCTION

Robin et al. [1994] described diffuse and massive brain destruction in a case of fetal hypomobility and raised the question of its cause and pathogenesis. We reported similar neuropathological findings on 3 unrelated fetuses with severe lethal akinesia [Encha Razavi et al., 1990]. Recently, 2 new cases in sibs with fetal akinesia sequence (FAS) have come to our attention, with similar primary neuronal "degeneration" affecting the brain and spinal cord.

This neuropathological pattern, although documented in the literature, has received little attention until recently. We propose calling this distinct, lethal entity, type III lissencephaly syndrome. Parental consanguinity and recurrence in sibs support the autosomal-recessive nature of the lesions. In this setting, the mechanism of neuronal death is not yet understood; abnormal apoptosis and/or deficiency in neurotropic factors may be considered possible causes.

CLINICOPATHOLOGICAL REPORTS

Recently, we studied the brain of a 24-week female fetus with FAS (case 5), born to nonconsanguineous and healthy parents, with a previously affected female fetus (case 4) and 2 healthy children. In case 4 pregnancy was terminated at 26 weeks of gestation for polyhydramnios and arthrogryposis. Autopsy and other fetal investigations were rejected in this case. However, a polaroid photograph confirmed severe arthrogryposis, associated with edema of the scalp and face (Fig. 1a). In case 5 (sister of case 4), fetal ultrasound screening performed at 23 weeks of gestation disclosed polyhydramnios and severe arthrogryposis with cerebral malformations (corpus callosum and vermian agenesis). Pregnancy was terminated at 24 weeks of gestation. The fetus had a normal karyotype and anomalies similar to those found in the index case, with craniofacial edema and arthrogryposis (Fig. 1b). Autopsy demonstrated pulmonary hypoplasia (7.92 g, Normal = 17 g). Neuropathological examination (Fig. 2) disclosed a smooth brain (normal for age), weighing 78.5 g (Normal = 98 g), with a hypoplastic brain stem and cystic cerebellum. Coronal sections confirmed the absence of the corpus callosum and presence of large ventricles, and disclosed severe bilateral multicystic periventricular lesions extending to the basal ganglia. Histological study mainly showed severe neuronal loss of the cortical plate, matrix zones, basal ganglia, brain stem nuclei, and spinal cord. This was associated with massive glial fibrillary acidic protein (GFAP)-positive, stellar astrocytic proliferation, multiple microinfarcts, and minute calcifications. All fibers and tracts were extremely reduced. Detection of apoptotic cells by in situ end-labeling of fragmented DNA strands (ApopTag™, Oncor, Gaithersburg, MD) in fixed cerebral tissue did not show any difference between this case and a control age-matched case.

Received for publication December 30, 1994; revision received February 28, 1995.

Address reprint requests to Férechté Encha Razavi, M.D., Service Histo-Neuropathologie, Hôpital Henri Mondor, 51 Bld. de Ml. de Lattre de Tassigny, Créteil, Cedex 94010, France.

Fig. 1. Fetal akinesia phenotype. **a:** Patient 4. **b:** Patient 5.

DISCUSSION

Intrauterine movement is now recognized as an essential factor for normal fetal development and morphogenesis. The fetal akinesia sequence (FAS), also called arthrogryposis multiplex congenita (AMC) [Banker, 1986], is a heterogenous group of conditions that may be caused by disorders of the developing motor system on all possible levels (cerebral, spinal, and neuromuscular), or by environmental insults to the fetus. FAS due to a CNS disorder is called neurogenic FAS (N-FAS) and represents most cases of FAS. In a prospective study of 89 infants and children with AMC, Banker [1986] considered 84 cases as neurogenic. On the other hand, Hall [1986] emphasized the heterogeneity of this entity, which may result from any neuropathic cause, primary or secondary (viral, toxic, maternal illness, etc.).

Among N-FAS, a heterogeneous group of "neurodegenerative" familial disorders deserves special attention. They may affect the developing nervous system at variable ages and levels (cerebral and/or spinal) [Banker, 1986]. We reported, in 3 unrelated fetuses of 26, 32, and 34 weeks of gestation with lethal FAS (Table I), a distinct neurodegenerative disorder affecting the cerebrum and the spinal cord (Figs. 3, 4), and raised the problem of its etiology and pathogeny [Encha-Razavi et al., 1990]. In all cases, severe external hydrocephalus and extreme micrencephaly (brain weight of 12 g, 20 g, and 25 g, respectively) were found in association with agyria/pachygyria and brain stem and cerebellar hypoplasia. Large ventricles were found in all cases with multicystic lesions (either in the subependymal region or in the brain stem) associated with diffuse ependymal abrasion and severe glial GFAP-positive reaction. Extensive vascularization, and a pronounced reduction of neurons with minute calcifications, were found in the cortical plate, basal ganglia, brain stem, and spinal cord. Fibers and tracts were extremely reduced in all cases, represented by separate fiber bundles. Electron microscope investigation performed in case 3 did not show evidence of specific abnormalities. Screening for toxoplasmosis and cytomegalovirus infection was negative in all cases. This pattern, although reported in connection with lethal FAS (as Neu-Laxova (NL) syndrome [Fitch et al., 1982], Pena-Shokeir phenotype [Erdl et al., 1989], or lethal multiple pterygium syndrome [Spearritt et al., 1993]), has received little interest until recently.

Banker [1986], in her prospective study of AMC, delineated the entity first (in 9 cases, with 4 sets of sibs) and called it "CNS dysgenesis." All cases in this group were described as having "a curtailment of the program of normal development of the CNS" characterized by microcephaly and hypoplastic brain stem with "reduction of neurons in the cerebral cortex, motor nuclei of the brain stem, and anterior horns of the spinal cord with thinned corticospinal and corticobulbar tracts."

Ostrovskaya and Lazjuk [1988] reported on 3 stillborn infants (2 sibs and a single case) of 39, 40, and 34 weeks of gestation, respectively, with similar neuropathological findings that they considered characteristic of NL syndrome (Table II). In all cases, severe microcephaly (20 g, 33 g, and 18 g, respectively) and lissencephaly with granular surfaces were reported with immature cortical plate, reduced in thickness, with focal polymicrogyria and immature small neurons with rare processes, intermingled with a considerable number of glial elements. Poorly differentiated basal ganglia with a decreased number of neurons in the nuclei of the brain stem, and hypoplasia of fibers and tracts, were also observed.

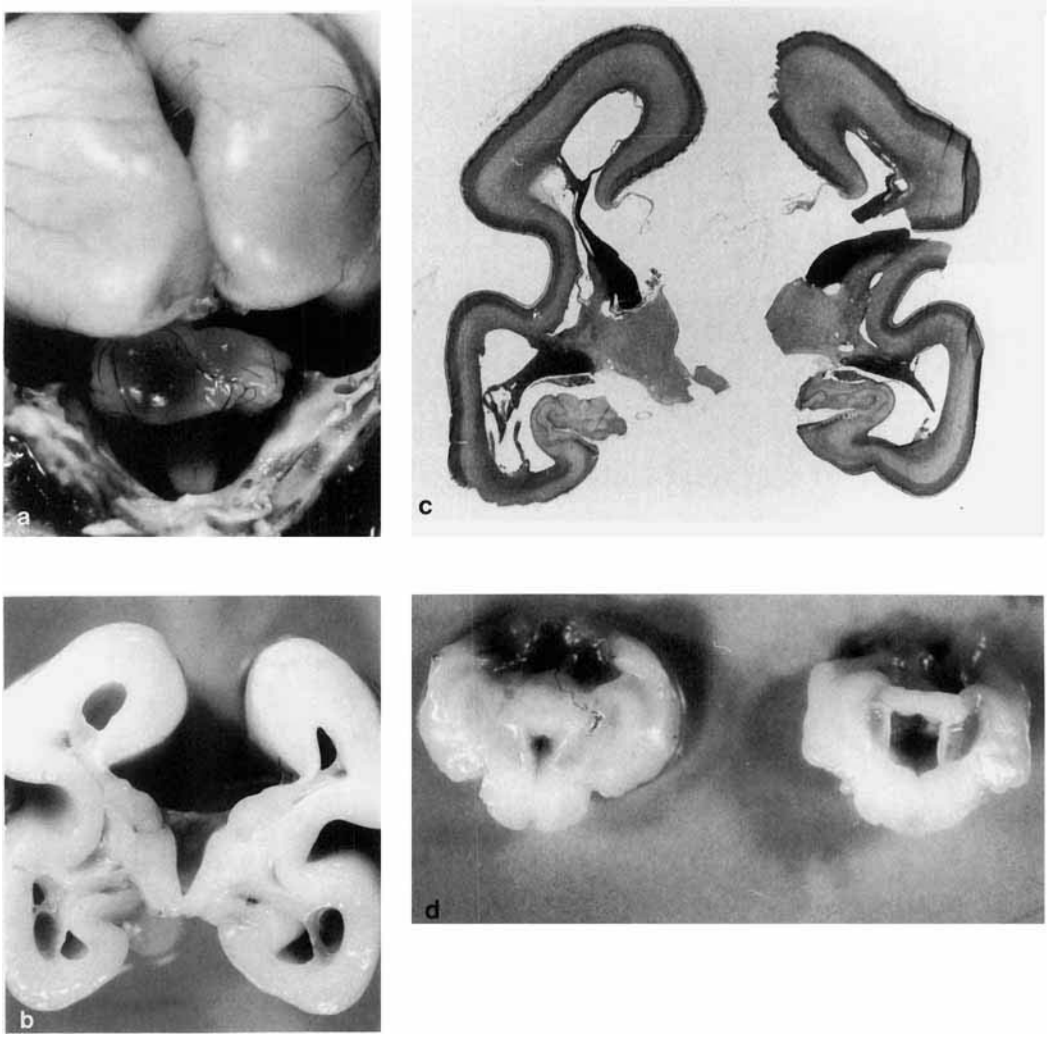

Fig. 2. Neuropathological findings, patient 5 (24 weeks of gestation). **a:** View of posterior fossa with cystic cerebellum. **b,c:** Coronal section of the brain and general view of celloidin-embedded hemispheres (H&E). Note ventricular dilatation, the absence of the corpus callosum (reduced to rare fibers), and massive periventricular cystic formations. **d:** Transverse section of the cerebellum. Note extensive cystic lesion.

Recently, of 3 fetuses (Table II) with NL syndrome, 2 sibs of 17 and 32 weeks, and a 39-week-gestational-age infant, died soon after birth; in all 3, Norman et al. [1994] reported mild microcephaly (10–15% of normal) with smooth-to-cobblestone brain surface with large subependymal cysts and abnormalities of the cortical ribbon, described as "a smooth band of unlaminated small cells, a rippled pattern, and more classic polymicrogyria with festooning of the cortical ribbon and an acellular intracortical band containing karyorrhectic

TABLE I. Clinicopathological Findings in Our Set of Type III Lissencephaly (n = 5)*

Patients	1	2	3	4–5 (sibs)
Consanguinuity	–	+	–	–
Sex	M	F	M	F, F
Weeks of gestation	26	32	34	26, 24
Birth weight (g)	300	748	890	690
OFC (cm)	17	24	25	24
Polyhydramnios	+	+	+	+
IUGR	+	+	+	+
Arthrogryposis (severe)	+	+	+	+
Pulmonary hypoplasia	+	+	+	+
Karyotype	Nl	Nl	Nl	Nl
Screening for infection (toxo, CMV)	–	–	–	–

* M, male; F, female; OFC, head circumference; IUGR, intrauterine growth retardation.

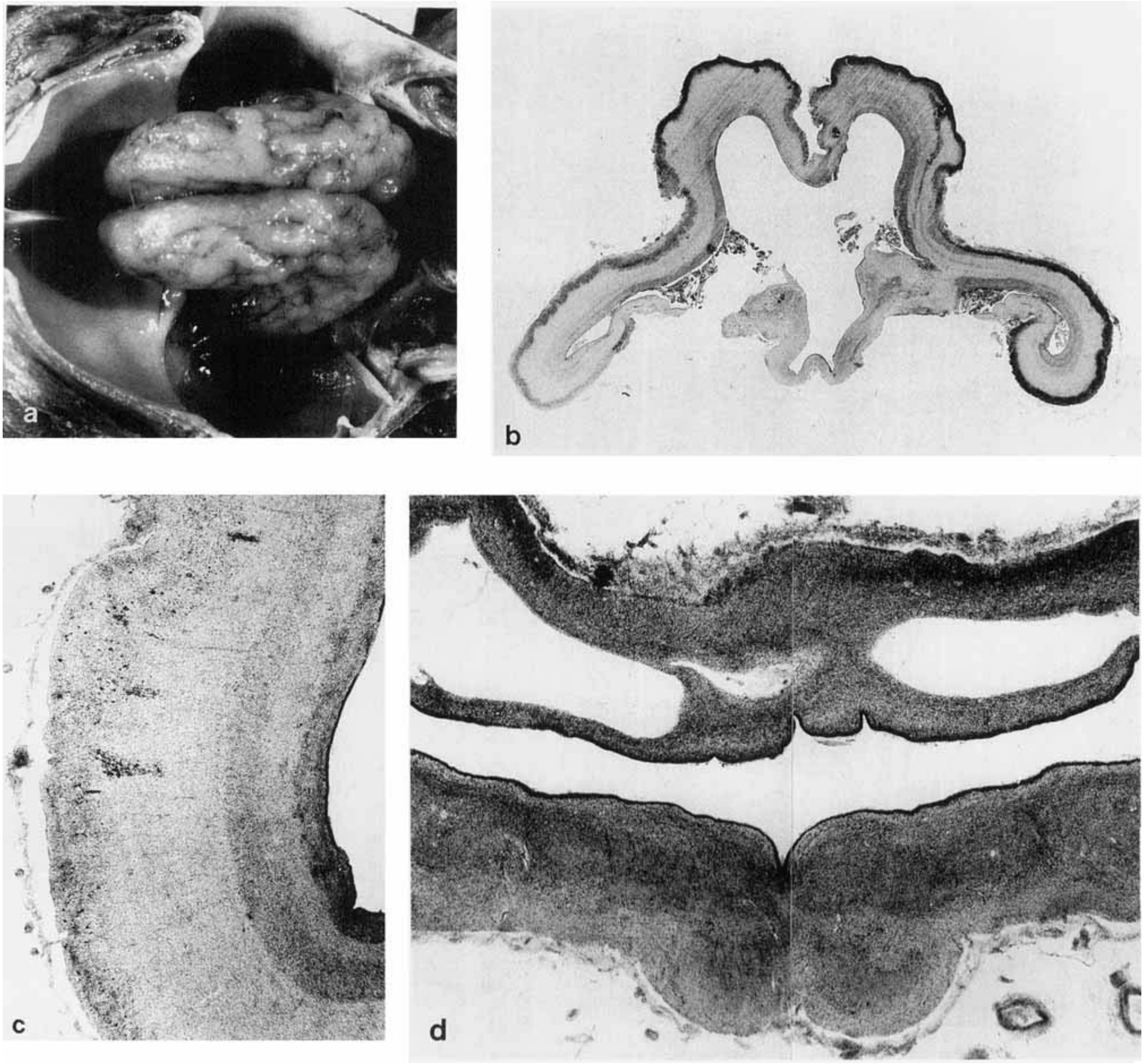

Fig. 3. Neuropathological findings, patient 2 (32 weeks of gestation). **a:** External configuration of the atrophic brain with a "walnut" granular pattern. Note severe external hydrocephalus. **b:** Coronal section (celloidin embedded, H&E). Note hypoplasia of the basal ganglia and internal hydrocephalus. **c:** Histopathological appearance of cerebral mantle (H&E, ×6.3). Note immature cortical plate, with heterotopias and microcalcifications. **d:** Histological appearance of the brain stem and the cerebellum (H&E, ×6.3). Note cystic formations, and absence of pontine nuclei, with fiber and tract rarefaction.

nuclei." All neurons, and in particular the intracortical neurons, were "small, and packed close together, suggesting failure of growth and maturation of the neuron cell body and failure of neuronal processes to grow normally in the cortex."

These findings are concordant with those reported by Robin et al. [1994] (Table II) in a newborn fetus of 28 weeks' gestation, markedly edematous with stiff joints and no spontaneous movements, who died on day 4. The brain weighed 130 g (Normal = 145 g), with well-formed hemispheres and "extensive cystic degeneration" of the basal ganglia and hemispheric white matter. A relatively well-preserved cortical ribbon was observed, with scattered mineralized neurons with karyorrhexis and gliosis. Widespread injury to the cerebellum (loss of internal granule cells and prominent gliosis), and marked neuronal dropout and gliosis, were also noted in multiple nuclei of the medulla and throughout the spinal cord.

The main pathological finding in this group of primary N-FAS is a diffuse neurodegenerative process, affecting both the cerebrum and the spinal cord, responsible for brain atrophy of variable severity, characterized by external and internal hydrocephalus, microcephaly,

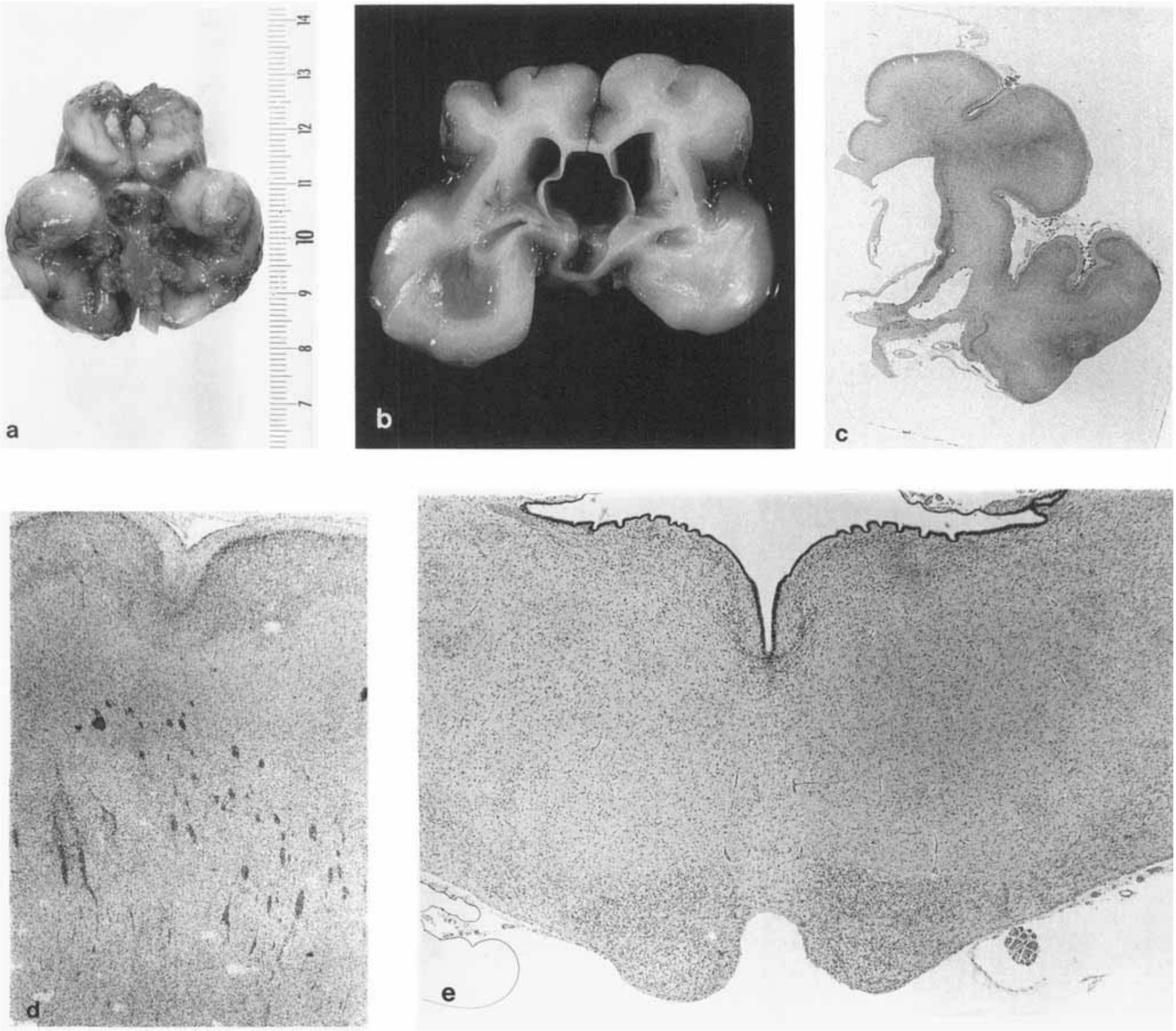

Fig. 4. Neuropathological findings, patient 3 (34 weeks of gestation). **a:** Basal view of atrophic pachygyric/agyric grain. **b:** Coronal section of brain. Note hypoplasia of the basal ganglia, hydrocephalus, and cystic formations. **c:** General view of one paraffin-embedded hemisphere (H&E). **d:** Details of immature cortical plate with heterotopias (H&E, ×16). **e:** Histological appearance of the pons (H&E, ×6.3). Note absence of pontine nuclei, with fiber and tract hypoplasia.

and gyral reduction. Microcephaly may be mild (10–15% of normal) as in our case 5 and as in Norman et al. [1994] and in Robin et al. [1994] cases or extreme (ratio of observed to expected brain weight below 0.3) as in our 3 first cases and as in Ostrovskaya and Lazjuk [1988] cases. Brain atrophy is also responsible for gyral changes. Convolutions may be well-preserved [Robin et al., 1994], coarse (pachygyric) (our case 3), or rare with a granular surface (our case 2, as well as Ostrovskaya and Lazjuk [1988], and Norman et al. [1994]).

Histologically, the classical pattern of neuronal degeneration from cell size reduction to karyorrhectic nuclei and cell death is found in the poorly cellular cortical plate, basal ganglia, brain stem, and anterior horns of the spinal cord. This is constantly associated with hypoplasia of fibers and tracts, resulting in hypoplastic brain stem and spinal cord. In this setting, screening for infectious agents was negative in all cases. Parental consanguinity in our case 2, and the recurrence of the entity in our case 5 and in those of Banker [1986], Ostrovskaya and Lazjuk [1988], and Norman et al. [1994], give support for the inherited (autosomal-recessive) nature of the lesions. Karyotypes were normal in all cases.

Until the genetic and/or metabolic defect(s) at the origin of these neurodegenerative lesions is found, we suggest calling this entity, type III lissencephaly. Lissencephaly (smooth brain), a descriptive term characteristic of agyria, is also applied to pachygyric brain

TABLE II. Neuropathological Findings in Four Sets of Patients With Type III Lissencephaly*

Series	I	II	III	IV
Brain atrophy				
Severe MC	3/4	3/3		
Mild MC	1/4		3/3	1/1
Agyria/pachygyria	3/4[a]	3/3	2/3[a]	
BG hypoplasia	4/4	3/3	3/3	1/1
BS hypoplasia	4/4	3/3	3/3	1/1
SC hypoplasia	4/4	3/3	3/3	1/1
Neuronal death (diffuse)	4/4	3/3	3/3	1/1
Tract rarefaction	4/4	3/3	3/3	1/1

* Series identification: I, Encha Razavi, 1995; II, Ostrovskaya and Lazjuk, 1988; III, Norman et al., 1994; IV, Robin et al., 1994. MC, microcephaly; BG, basal ganglia; BS, brain stem; SC, spinal cord.
[a] Physiologically smooth brain.

which differs from agyria only in severity [Friede, 1985]. Two distinct types are now well documented [reviewed in Encha-Razavi, 1995]. Type I lissencephaly, also associated with microcephaly, is a well-known migratory disorder mainly characterized by the reversal of the normal gray-white matter ratio, with a four-layered cortex and an ectopic layer II. Type I lissencephaly is the major manifestation of malformative entities such as the Miller-Dieker syndrome, Norman-Roberts syndrome, and isolated lissencephaly syndrome [Dobyns et al., 1984]. The existence of a chromosome marker on 17p13.3 may help for syndrome identification in Miller-Dieker syndrome [Oostra et al., 1991]. Few reports support the existence of other syndromes with type I lissencephaly and extreme microcephaly [Barth et al., 1982]. However, FAS has not been documented in any of these syndromes.

Type II lissencephaly, also called cortical dysplasia, is a distinct cytoarchitectonic disorder mainly characterized by the obliteration of the subarachnoid space with neuroglial ectopic tissue, responsible for thick opaque meninges and hydrocephalus. Type II lissencephaly is the specific component of at least two familial syndromes, i.e., Walker-Warburg syndrome and Fukuyama congenital muscular dystrophy [Dobyns et al., 1985a].

The term type III lissencephaly was first introduced by Dobyns et al. [1984, 1985b] to describe micrencephalic agyric brains in NL syndrome. We suggest enlarging this definition to the entity described herein, as characterized by the distinct neurodegenerative lesions of the cerebrum and spinal cord responsible for FAS.

Among cases of FAS, only a detailed neuropathological study permits the identification of lesions characteristic of type III lissencephaly syndrome. Usually, the entity is reported under a constellation of eponyms and acronyms, such as NL syndrome [Fitch et al., 1982; Ostrovskaya and Lazjuk, 1988; Norman et al., 1994], Pena-Shokeir phenotype [Erdl et al., 1989], lethal multiple pterygium syndrome [Spearritt et al., 1993], and others [Robin et al., 1994]. The literature focuses on the confusion which remains concerning the nosology of these entities, and raises the question of whether these phenotypes are separate entities [Fitch et al., 1982; Hall, 1986; Gershoni-Baruch et al., 1991]. Clinically, all reported cases display to various degrees a spectrum of abnormalities characterized by polyhydramnios, growth retardation, short umbilical cord, skin abnormalities (excessive dryness suggestive of ichtiosis, with subcutaneous edema), micrognathia, pulmonary hypoplasia, and skeletal abnormalities (thin and elongated bones). Our knowledge of these diseases has much improved thanks to Moessinger [1983], who demonstrated that rat fetuses paralyzed by curare develop in utero similar abnormalities (multiple joint contracture, pulmonary hypoplasia, micrognathia, growth retardation, short umbilical cord, short bowel, polyhydramnios, and skin abnormalities). He considered these abnormalities the consequence of fetal akinesia, and coined the term "fetal akinesia deformation sequence." The current concept in these entities is to consider the cascade of malformations, first described as distinctive of NL syndrome [Neu et al., 1971] and Pena-Shokeir phenotype [Pena and Shokeir, 1974], as secondary deformations due to fetal akinesia [Hall, 1986; Rodriguez and Palacios, 1991; Vuopala and Herva, 1994].

FORMULATION OF HYPOTHESIS

Type III lissencephaly apparently results from a degenerative process affecting neuronal survival at both cerebral and spinal levels. It may be postulated that in this setting, neuronal multiplication and migration follow the normal program of development. The well-formed cortical plate, although poorly cellular and immature, accords with a normal program of cell multiplication and migration. Neuronal rarefaction in the cortical plate may be due to destruction of migrating cells in the devastated germinal zones, and/or may result from in situ destruction after the settlement of the cortical plate. The immature cortical plate (without laminar stratification) could be considered the result of delayed neuronal maturation, which occurs classically between 16–26 weeks of gestation. Hypoplasia of fibers and tracts would result from lack or failure of neuronal processes to grow.

Norman et al. [1994] explained this pattern of "abnormal excessive death of primitive neuroectodermal cell" by abnormal apoptosis. In our case 5, detection of apoptotic cells by in situ end-labeling of fragmented DNA strands (ApopTag™, Oncor) in fixed cerebral tis-

sue did not show any difference between our case and a control age-matched case.

In CNS degeneration, the role of epigenetic factors such as neurotrophic factors has been neglected until recently. Neurotrophic factors may mediate neuronal proliferation, migration or differentiation, growth, and maintenance. The ciliary neurotropic factor [CNTF), *identified* in 1989, plays a major role in the maintenance of the motor neuron of the spinal cord [Lin et al., 1989]. In the *pmn/pmn* mouse, which is an animal model for human spinal motor neuron disease (a heterogenous group of neurodegenerative disorders that may affect the brain stem and the spinal cord at any age), the preventive role of the CNTF has been demonstrated [Sendtner et al., 1992]. Moreover, studies indicate that suppression of CNTF activity in transgenic homozygote mice *CNTF−/CNTF−* does not interfere with motor neuron formation, but leads to their secondary degeneration and progressive reduction in muscle strength [Masu et al., 1993]. Similar molecular and experimental approaches in type III lissencephaly will help improve understanding of the mechanism of neuronal survival in the CNS during fetal life.

REFERENCES

Banker BK (1986): Congenital deformities. In Engel AG, McKnight WL, Banker BQ (eds): "Myology Basic and Clinical." New York: McGraw-Hill Book Company, pp 2109–2159.

Barth PG, Mullaart R, Stam FC, Slooff JP (1982): Familial lissencephaly with extreme neopallial hypoplasia. Brain Dev 4:145–151.

Dobyns WB, Stratton RF, Greenberg F (1984): Syndromes with lissencephaly. I: Miller-Dieker and Norman-Roberts syndromes and isolated lissencephaly. Am J Med Genet 18:509–526.

Dobyns WB, Kirkpatrick JB, Hittner HM, Roberts RM, Kretzer FL (1985a): Syndromes with lissencephaly. II: Walker-Warburg and cerebro-oculo-muscular syndromes and a new syndrome with type II lissencephaly. Am J Med Genet 22:157–195.

Dobyns WB, Gilbert EF, Opitz JM (1985b): Letter to the editor. Further comments on the lissencephaly syndromes. Am J Med Genet 22:197–211.

Encha Razavi F (1995): Fetal neuropathology. In Duckett S (ed): "Pediatric Neuropathology." New York: Williams & Wilkins, pp 108–122.

Encha Razavi F, Larroche JC, Roume J, Gonzales M (1990): A new type of "lissencephaly" with extreme micrencephaly, immature cortical plate, and severe calcifications. J Neuropathol Exp Neurol 49:304 (abstract).

Erdl R, Schmidtke K, Jakobeit M, Nerlich A, Schramm T (1989): Pena-Shokeir phenotype with major CNS malformations: Clinicopathological report of two siblings. Clin Genet 36:127–135.

Fitch N, Resch L, Rochon L (1982): The Neu-Laxova syndrome: Comments on syndrome identification. Am J Med Genet 13:445–452.

Friede RL (1989): "Developmental Neuropathology." Berlin: Springer-Verlag, pp 330–346.

Gershoni-Baruch R, Ludatsher RM, Lichtig C, Sujov P, Machoul I (1991): Cerebro-oculo-facio-skeletal syndrome: Further delineation. Am J Med Genet 41:74–77.

Hall JG (1986): Invited editorial comment: Analysis of Pena-Shokeir phenotype. Am J Med Genet 25:99–117.

Lin LFH, Mismer D, Lile JD, Armes LG, Butler ET III, Vannice JL, Collins F (1989): Purification, cloning, and expression of ciliary neurotrophic factor (CNTF). Science 246:1023–1025.

Masu Y, Wolf E, Holtmann B, Sendtner M, Brem G, Thoenen H (1993): Disruption of the CNTF gene results in motor neuron degeneration. Nature 365:27–32.

Moessinger AC (1983): Fetal akinesia deformation sequence: An animal model. Pediatrics 72:857–863.

Neu RL, Kajii T, Gardner LI, Nagyfy SF, King S (1971): A lethal syndrome of microcephaly with multiple congenital anomalies in three siblings. Pediatrics 47:610–612.

Norman MG, White VA, Dimmick JE (1994): Pathology of Neu-Laxova syndrome. Brain Pathol 4:394 (abstract).

Oostra BA, de Rijk-van Andel JF, Eussen HJ, van Hemel JO, Halley DJJ, Niermeijer MF (1991): DNA analysis in patients with lissencephaly type I and other cortical dysplasias. Am J Med Genet 40:383–386.

Ostrovskaya TI, Lazjuk GI (1988): Cerebral abnormalities in the Neu-Laxova syndrome. Am J Med Genet 30:747–756.

Pena SDJ, Shokeir MHK (1974): Syndrome of camptodactyly, multiple ankylosis, facial anomalies and pulmonary hypoplasia: A lethal condition. J Pediatr 85:373–375.

Robin NH, Curtis MT, Mulla W, Reynolds CA, Anday E, Rorke LB, Zackai EH (1994): Non-immune hydrops fetalis associated with impaired fetal movement: A case report and review. Am J Med Genet 53:251–254.

Rodriguez JI, Palacios J (1991): Pathogenetic mechanisms of fetal akinesia deformation sequence and oligohydramnios sequence. Am J Med Genet 40:284–289.

Sendtner M, Schmalbruch H, Stöckli KA, Caroll P, Kreutzberg GW, Thoenen H (1992): Ciliary neurotrophic factor prevents degeneration of motor neurons in mouse mutant progressive motor neuropathy. Nature 358:502–504.

Spearritt DJ, Tannenberg AEG, Payton DJ (1993): Lethal multiple pterygium syndrome: Report of a case with neuropathological anomalies. Am J Med Genet 47:45–49.

Vuopala K, Herva R (1994): Lethal congenital contracture syndrome: Further delineation and genetic aspects. J Med Genet 31:521–527.